Patent
MSB-7213

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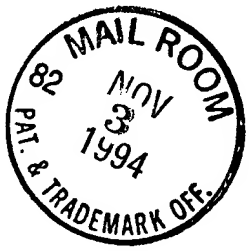

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	PETRA BOYLE GAYLE D. WETZEL KENNETH J. LEMBACH	)	APPEAL BRIEF
Serial No.:	08/026,957	)	
Filed:	March 5, 1993	)	Examiner: R. Budens
For:	HUMAN ANTI-TNF ANTIBODIES	)	Art Unit: 1806

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Commissioner of Patents and Trademarks
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Dear Sir:

This is a Brief (3 copies) supporting an Appeal from the final rejection on April 19, 1994 of Claims 1-14 in the above entitled application. Please charge deposit account 03-4000 the sum of $280.00 under 37 5CFR 1.17(f) as authorized in the enclosed Deposit Account Authorization Form.

STATUS OF ALL CLAIMS: The claims of this Appeal are shown on the attached Appendix. The claims correspond to original claims 1-14 except that claims 1, 11, 12 and 13 have been amended.

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STATUS OF AMENDMENTS AFTER FINAL: In a Request for Amendment after the Final Rejection, the Applicants requested an amendment to Claim 1 and amendments to the Specification to show a cell line deposit. In an Advisory Action mailed August 22, 1994 the Examiner indicated those amendments would be entered upon filing an Appeal.

SUMMARY OF THE INVENTION: The invention is human monoclonal antibodies (mAbs) that bind specifically to human tumor necrosis factor-α (TNFα). Such antibodies of both the IgM and IgG isotypes have been made and characterized. A representative mAb binds to cell surface TNFα (csTNFα) on a variety of human cells. The binding to csTNFα was demonstrated to be specific since it can be inhibited by TNFα but not by TNFß, a neutralizing mouse anti-TNFα mAb, or by a recombinant form of the extracellular domain of the p55 TNF receptor (TNFR). Human monoclonal anti-TNFα antibodies that bind to human TNFα are inherently unnatural and no prior art has been found or applied showing or suggesting such antibodies were possible.

ISSUES FOR REVIEW:

I Whether the rejection of Claims 1-14 under 35 U.S.C. §101 for provisional double patenting should be maintained.

2 Whether Claims 1-14 should have been rejected under 35 U.S.C. §101 because the specification does not include a disclosure of utility.

3 Whether Claims 1-14 and the Specification should have been rejected under 35 U.S.C. §101 and §112 (second paragraph) on the grounds that the Applicants did not specifically teach one skilled in the art how to use the invention;

4 Whether the Specification should have been rejected under 35 U.S.C. §112 (first paragraph) for failing to provide an enabling disclosure setting forth evidence of utility and whether claims 1-14 should have been rejected for that reason.

5 Whether Claims 1-14 and the Specification should have been rejected under 35 U.S.C. §112 for failing to provide a chain of custody for cell lines that were deposited with the ATCC after the filing date.

GROUPING OF CLAIMS FOR EACH ISSUE: With the possible exception of issue 5 above as applied to claim 11 (cell line deposit) the Examiner has applied all bases for rejection against each of claims 1-14. Applicants request that each of claims 1-14 be considered separately under each of the rejections under 35 U.S.C. §101 and 35 U.S.C. §112 (first paragraph) for reasons given below.

EXAMINER'S ARGUMENTS

THE REJECTION UNDER 35 U.S.C. §101: The Examiner rejected Claims 1-14 for provisional double patenting after a Continuation-In-Part Application containing the same claims was filed.

Claims 1-14 were also rejected because the Examiner believed an intended utility had not been disclosed in the Specification. The Examiner relied on In re Kirk and Petrow (153 U.S.P.Q. 49 (CCPA 1967)) for the position that utility by analogy is not persuasive.

THE REJECTIONS UNDER 35 U.S.C. §112 (first paragraph): The Examiner rejected Claims 1-14 and the Specification because the Applicants had not disclosed any intended utility (see §101 rejection). The Examiner's position appears to be that one skilled in the art would not be able to use the invention without undue experimentation.

Claims 1-14 and the Specification were also rejected because the Examiner believed that the Specification failed to adequately provide an enabling disclosure with respect to the scope of the claims. The Examiner believed that the number of potential donors for human mAbs against TNFα is low and therefore it would be unlikely that one skilled in the art would be able to obtain human antibodies against TNFα without undue experimentation.

The Specification was also rejected under 35 U.S.C. §112 (first paragraph) because the Examiner believed that a chain of custody for cell lines that were deposited with the ATCC after the filing date had not been established.

The Examiner acknowledged that Claims 1-14 appear free of the prior art in that the prior art does not disclose the production of human monoclonal antibodies to human TNFα.

APPELLANTS ARGUMENTS AND REASONS FOR PATENTABILITY:

Re 35 U.S.C. §101: Provisional Double Patenting. The Applicants acknowledge the provisional double patenting rejection but would like to postpone a formal response to that rejection until there is a determination of the final status of claims in this Application and co-pending CIP Application Serial No. 145,060 at which time Applicants would, if necessary, file a Terminal Disclaimer to address any double patenting issue.

Specific Utility. The Examiner claims the situation here is similar to that of Kirk and Petrow, 153 USPQ 49 at 52 (CCPA, 1967). That decision is clearly distinguishable. The synthetic steroid intermediates of that decision are not monoclonal antibodies. The inventors in Kirk and Petrow relied on the structural similarity between the claimed steroid intermediates and those known to be useful for an inference of utility. Because the inventors had not tested the claimed steroids, the CCPA held the inventors could not claim the intermediates could be used in the same manner as the analogous intermediates.

In the instant invention, the Applicants have tested the claimed mAbs in functional assays and found them to react similarly to other mAbs against TNFα. Therefore, there is more than just the assumed similarity between different mAbs which react to the same antigen, but also a showing that the antibodies disclosed in the invention do react similarly.

In addition, the CCPA in Kirk and Petrow pointed out that the Applicants had not made any statements of utility in the Specification but merely stated that the intermediates had "biological activity". In the instant Application, the Applicants have not only stated that the antibodies have biological activity, they have indicated in the embodiments some specific uses of the antibodies. The antibodies have been found to be useful in Western Blot Assays, ELISAs, and FACS staining to name just a few.

It should be noted that in a vigorous and separately written dissent in Kirk and Petrow by Judge G. Rich, 153 USPQ 266 at 273, the requirement of mentioning a specific use was applicable (only) "...at least in the absence of evidence that a specific use would be obvious." (underlining added). That dissent rationale is analogous to the present situation. It is well known to those skilled in the art of monoclonal antibodies that any monoclonal antibody can be used to bind to a given substance. These uses may have many forms such as diagnostic uses, purification, therapeutic uses, etc.

The Examiner appears to have taken the position that under both 35 USC §101 and §112, first paragraph, the Applicants are required to teach how to use the claimed invention and have not done so. It is the Applicants' position that they have done this in their specification as filed. In further support of this position, the Applicants enclosed a Declaration under 37 CFR 1.132 by Professor Matthias Wabl, a person skilled in the art, pointing out that specific uses of the human anti-TNFα antibodies would be obvious. The declaration from Dr. Matthias Wabl points out that "a variety of specific uses would immediately be obvious to a person skilled in the art. [A]ny monoclonal antibody, once generated, can be used in a

variety of immunoassays which would be inherently useful for not only research but as diagnostic tools." The Examiner was not persuaded by the declaration, stating that the "evidence of Wabl represents Opinion declaration and the evidence is not convincing". The Applicants believe that Dr. Wabl, as shown by his education and experience in the field, is a suitable declarant as to the usefulness of human monoclonal antibodies against TNFα and the Examiner's rejection of his opinion is not warranted.

For further evidence of utility, see especially the Abstract (attached to the Wabl Declaration) by J. Wherry, et al. presented at the 3rd ICAAC, October 17-20, 1993 showing a trend toward efficacy in using murine anti-TNF to treat such patients. A fortiori, a human anti-TNF would be expected to have at least a similar trend and, being human, more desirable to avoid potential immunogenicity problems. See also the copies of the news article describing clinical studies of anti-TNF and catalogs showing that anti-TNF antibodies are commercially available. It is submitted that commercial availability is per se evidence of utility of a given monoclonal antibody. Since anti-TNF monoclonals are in fact commercially available, it is submitted such antibodies are inherently useful.

Re 35 U.S.C. §112 (first paragraph): The Examiner rejected the Specification and Claims 1-14 on the grounds that because the Application failed as a matter of fact to establish utility under 35 U.S.C. §101, the Application fails as a matter of law under 35 U.S.C. §112. See In re Ziegler, 26 USPQ 2d 1600 at 1603 (CAFC 1993). The Applicants submit they have satisfied 35 U.S.C. §101 (see above) and also have satisfied 35 U.S.C. §112. In the embodiments, the Applicants described protocols they used with the antibodies to perform Western Blots, FACS analysis and other assays. In addition, the wide availability of antibodies to TNFα indicates that one skilled in the art would be familiar with various other uses of antibodies.

The Examiner rejected the Specification on the grounds that under 35 U.S.C. §112 (first paragraph) the Application failed to provide an enabling disclosure with respect to the scope of the claims. Apparently, the Examiner mistakenly believed that all of the antibodies listed in Table 1 of the Specific Embodiments originated from one donor. In fact, as disclosed in Declaration #1 filed by Dr. Wetzel (copy enclosed), the human antibodies originated from five donors. The Examiner also mistakenly believed that none of the other antibodies exhibit the same cell binding attributes as B5. While B5 is the apparent "best" of the antibodies assayed, other antibodies such as H5 and 7T1 bound to cells in a cell surface binding assay (see Table 7 at page 28 of the specification). These antibodies were derived from tonsillar tissue of two different donors and were polyreactive but have the highest affinity for TNF. Therefore, at the least, these two antibodies share some of the attributes of B5. The antibody F12, which is not from the same donor as B5, exhibited the same degree of binding to TNF as B5 (see Table 1 at page 13) but because B5 had been discovered first, F12 was not characterized further.

The Examiner used the absence of other "B5-type" antibodies as evidence that one skilled in the art could not reproduce the invention. The Applicants did not find other "B5-type" antibodies because, as is usual in the art, they used a preliminary screening assay to find an antibody that had the desired characteristics and from then on only that antibody was characterized. The antibodies that did not perform as well as B5 in the initial assay were not selected for further study. Therefore, it is possible that some other antibodies against TNF share the same attributes as B5 but were not found because they were not characterized as fully.

The Examiner was concerned that a CMV+ donor was needed to repeat the invention and that CMV+ donors are rare. The enclosed Declaration #1 by Dr. Wetzel clarifies the issue in that a CMV+ donor is probably not required and in any event, would not be hard to find.

He reiterates that the donors weren't screened for autoantibodies to TNF and therefore the presence of such antibodies is not necessary for the invention.

On page 4 of his Declaration, Dr. Wetzel explains that "[m]aking hybridomas is not unpredictable. One may have a somewhat low probability of obtaining exactly the same monoclonal antibody..." But "[i]t is quite common to obtain several different antibodies which are similar in their binding to antigen properties." Finding these antibodies requires screening of thousands of B-cell cultures. This screening procedure can be somewhat automated and made practical by the use of micro-titer plates.

The Court of Appeals for the Federal Circuit in In re Wands, 8 USPQ 2d 1400 (1988) stated the test to be used when determining undue experimentation for the preparation of mAbs.

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art.... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

See Wands, 8 USPQ 2d at 1404.

In further defining what is not undue experimentation in mAb preparation, the Court in Wands concluded: "The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." 8 USPQ at 1406.

In summary, to reproduce the instant invention, there are no special requirements of the donors which might make them hard to find. The only experimentation that must be done to make human mAbs against TNFα is screening of hybridomas, which according to Wands is not considered undue experimentation.

Re Chain of Custody: The Examiner rejected the Specification and Claims 1-14 on the grounds that a chain of custody for the deposited cell lines had not been established. The enclosed Declaration #2 of Dr. Wetzel, in paragraph 5, provides a chain of custody by stating under oath that the cell lines deposited are identical to the corresponding hybridomas described and were in his possession at the time the Application was filed.

CONCLUSION

The claims in this Application define patentable subject matter and they should have been allowed under both 35 U.S.C. § 101 and 35 U.S.C. § 112 (first paragraph).

Respectfully submitted,

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Date

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